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(54) PROCESS FOR THE PRODUCTION OF LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

(71) We, ORSYMONDE, a French Body Corporate of 17 Faubourg Montmartre, Paris 9e, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the production of pharmaceutical compositions.

It is well known that lyophilized products invariably have a fragile structure and are furthermore generally extremely hygroscopic. These two properties make them difficult to handle in an environment of normal humidity and make it necessary to use perfectly sealed packages for them.

It is known, for example, from British Patent Specifications Nos. 1,057,940 and 1,153,092 that compositions suitable for therapeutic applications can be obtained by freeze-drying or lyophilizing compositions containing medicaments. The first-mentioned patent is concerned with the production of pharmaceutical compositions for oral administration by lyophilizing a colloidal dispersion of a water-soluble, orally active mineral medicament, such as aluminium phosphate, aluminium hydroxide, aluminium carbonate, bismuth oxide, bismuth hydroxide, silica, carbon or silver, in an aqueous medium containing a physiologically acceptable organic gelling agent. The second patent is concerned with the production of pharmaceutical compositions suitable for parenteral administration by freeze-drying a sterile solution of mannitol in pyrogen-free water.

We have been investigating the production of pharmaceutical compositions comprising orally administrable organic medicaments such as liver extracts, vitamin C and arginine acid aspartate which have been dehydrated or desolvated by lyophilization to find forms capable either of resuming their original form when solvent is provided, or dissolving rapidly and completely in water, and which have improved mechanical strength in relation to the straight lyophilized form of the organic medicament itself and also have a slower moisture uptake.

As a result of research and experimentation it has now been found that pharmaceutical compositions comprising a liver extract, vitamin C or arginine acid aspartate and having the properties just mentioned above can be produced by lyophilization of a mixture of such a medicament with a lyophilization adjuvant comprising two ingredients, one of colloidal nature and the other a water-soluble physiologically innocuous filler (otherwise called an "extender" or "excipient"). The term "lyophilization" is used herein in its normal context to signify dehydration of a frozen substance by sublimation of H_2O *in vacuo*.

The present invention is therefore concerned with a process for producing a lyophilized pharmaceutical composition suitable for oral administration which comprises mixing a medicament selected from liver extracts, vitamin C and arginine acid aspartate, in the presence of water with a lyophilization adjuvant comprising (a) at least one substance selected from non-toxic hydrophilic colloids, polysaccharides and polymers of high molecular weight capable of yielding aqueous colloidal solutions, and (b) at least one water-soluble, edible, crystallisable, physiologically innocuous filler, and lyophilizing the mixture obtained.

The lyophilization adjuvants used in the new process must have such physical properties that their addition cannot interfere with the proper course of the lyophilization operation. Thus, they must not lower the freezing point of the material to be lyophilized to a level where melting would occur during the lyophilization. As these substances must be considered to be excipients for the pharmaceutical compositions, it is essential for them to have no effect on the medicament and to be physiologically innocuous.

Suitable colloidal substances comprising

part of the lyophilization adjuvant are gum arabic, alginates and pectinates, polyvinylpyrrolidone, polyethylene glycols, and sodium carboxymethylcellulose; and suitable fillers for the said adjuvant are lactose, glycine, mannitol, sorbitol, glucose, and sucrose. Amongst the fillers lactose, which normally contains one molecule of water, loses this during the lyophilization and can, as a result, play the role of a dehydrating agent in the lyophilized product.

Suitable proportions of colloidal substances and filler added to a solution of the material to be lyophilized make it possible to obtain a lyophilized product which is consistent, stable under normal ambient conditions, and entirely soluble and devoid of any toxicity (other than any toxicity of the medicament itself).

Variations in the amount of the lyophilization adjuvant make it possible to achieve any desired degree of hardness and solubility of the lyophilized product.

The lyophilized product obtained can be mechanically divided into pieces of well-defined shape and volume, which can be packed individually or in groups.

The pharmaceutical compositions obtained by the new process can be classified alongside effervescent entirely water-soluble tablets while avoiding the use of large amounts of alkaline excipients, or alongside drinkable ampoules, having an advantage in cost price, or alongside any liquid form, having a definite advantage of lower volume and weight for a given dosage and showing great stability and excellent storage characteristics.

In the new process, the lyophilization adjuvant is added to the organic medicament to be lyophilized in the presence of a small amount of water, at ordinary temperature, and the resulting solution or paste is subsequently lyophilized in a manner known *per se*. If the mixture to be lyophilized is too liquid, because of the choice of the proportions of the constituents or for other reasons, and a separation takes place during mixing, the mixture is frozen with continuous stirring and when a pasty consistency has been achieved the mixture is spread on the previously cooled plates of the lyophilization apparatus.

In one embodiment of the new process, the mixture to be lyophilized has added to it a substance capable of maintaining the organic medicament and lyophilization adjuvant—when mixed together in the presence of water—in the form of a foam, i.e. the added substance is a foam stabilizer, and the mixture is converted into a stable foam before lyophilization. Advantageously the foam stabilizer is a block polymer of ethylene oxide, propylene oxide and ethylene glycol of molecular weight between 7500 and 8250, of the formula:

$$HO(C_2H_4O)_x(C_3H_6O)_yC_2H_4O)_zH$$

(where x, y and z are integers) in which the $(C_3H_6O)_y$ portion has a molecular weight of 1500 to 1800 and the $(C_2H_4O)_{x+z}$ portion represents 80—90% by weight of the polymer. This embodiment is particularly advantageous for the preparation of a lyophilized composition containing vitamin C. It is all the more unexpected because it is known that vitamin C cannot be lyophilized by itself but melts, regardless of the lyophilization conditions, forming a varnish on the cooled surfaces of the lyophilization apparatus, without a continuous solution, thereby resisting lyophilization.

Preferred lyophilization adjuvants for liver extracts are mixtures of gum arabic and glycine or gum arabic and lactose. With liver extracts a suitable mixture for lyophilization consists of 4 parts of liver extract, 15 parts of water, 1 part of gum arabic and 60 parts of glycine or of lactose.

Preferred lyophilization adjuvants for vitamin C are mixtures of gum arabic and glycine. With vitamon C a suitable mixture for lyophilization consists of 0.1 to 0.5 parts of vitamin C, 0.3 part of water, 1.1 part of glycine, 0.06 part of gum arabic, and 0.05 part of a polymer of the formula specified above. The relationship of the parts indicated above are by weight.

Another embodiment of the invention relates to the preparation of effervescence pharmaceutical compositions. Effervescent pharmaceutical compositions have hitherto been prepared by a dry method, by combining a medicament in the anhydrous form with a mixture of ingredients capable of producing effervescence when added to water (hereinafter for the sake of brevity termed "an effervescent mixture") consisting of two anhydrous powders, one containing a non-toxic organic acid such as e.g. citric acid, tartaric acid or ascorbic acid, and the other containing a mineral carbonate or bicarbonate such as an alkali metal or alkaline earth metal carbonate or bicarbonate, especially neutral sodium carbonate or sodium bicarbonate, calcium carbonate, or magnesium carbonate. The mixture thus obtained is shaped into tablets and stored with exclusion of moisture. When introduced into water, it dissolves, causing an effervescence due to copious evolution of carbon dioxide.

The process of this invention for making such effervescent compositions is a "wet" process, in which the constituents of the effervescent mixture are added to the mixture to be lyophilized, at a temperature below 0°C. and sufficiently low to prevent any reaction between the constituents of the effervescent mixture, and the paste obtained is subsequently lyophilized.

Such a process has many advantages. It makes it possible to obtain lyophilized compositions which are completely water-soluble, because no water-insoluble excipients used as

lubricants for tablet making (e.g. talc and stearates) are employed. Desiccation by lyophilization yields dryer products than those obtained by conventional drying processes without reaching temperatures which present the danger of altering any heat-labile active medicaments present in the composition.

This embodiment of the invention is of particular importance to the production of lyophilized compositions containing arginine acid aspartate, for which the filler component of the lyophilization adjuvant is preferably a mixture of lactose and sucrose. Advantageously an effervescent mixture of citric acid and sodium bicarbonate is added to the arginine acid aspartate before lyophilization.

The invention is illustrated by the following Examples.

Example 1

In this Example, the manufacture of a medicine based on liver extract is described. The same process can also be applied to the other medicaments.

The starting point is a commercially available liver extract for drinkable preparations in the form of a soft extract containing 82% of solids, and having a degree of concentration of 25.

Small lyophilization containers, of parallelopiped shape and of size 5 cm × 5 cm × 3 cm, made of an aluminium foil of 50 microns thickness, are used. The surface which is in contact with air is thus 5 × 5 = 25 cm². The small containers, numbered 1 to 5, are filled as follows:

No. 1 — Solution:

Liver extract, 1:=25	4 g
Water	to 50 ml

No. 2 — Homogeneous paste obtained by triturating in a mortar:

Glycine	60 g
Gum arabic in powder form	1 g
Water	15 ml

No. 3 — The same paste as 2, in which the glycine is replaced by lactose.

No. 4 — The same paste as 2, but with 4 g of liver extract dissolved in the 15 ml of water.

No. 5 — The same paste as 3, to which 4 g of liver extract have been added.

Table I below summarises the composition of the contents of the small containers before lyophilization and gives the net dry weights of the products obtained after lyophilization.

TABLE I

Small Containers	No. 1	No. 2	No. 3	No. 4	No. 5
Liver extract	4 g			4 g	4 g
Glycine		60 g		60 g	
Lactose			60 g		60 g
Gum arabic		1 g	1 g	1 g	1 g
Water	50 ml	15 ml	15 ml	15 ml	15 ml
Weight after lyophilization	2.30 g	61 g	61 g	63.30 g	63.30 g

The temperautre and pressure conditions used during the lyophilization are given in Table II below.

After the lyophilization, the small containers are weighed at intervals which during the first six hours are initially closely spaced, and the moisture uptakes are expressed, in Table III below, in milligrams of water taken up by the contents of the small containers, the adjacent column giving the percentage of water in the product.

The examination of the results shows that during the first hours the moisture uptake of the liver extract in lactose (No. 5) or in glycine (No. 4) is very slight relative to (that of) the lyophilized extract (No. 1), because the 2.30 g of dry extract only take up 11 mg after 4 hours in lactose (**) and 52 mg after 4 hours in glycine (*), while the lyophilised extract (No. 1) had taken up 131 mg, representing 5.7% of water, as against 0.153% for the mixture of lactose+liver and 0.2% for the mixture of glycine+liver.

This shows that the very hygroscopic products are protected against a rapid moisture uptake, which allows them to be handled

without taking many precautions and furthermore their low water content ensures that they store excellently. Furthermore, lactose has proved superior to glycine.

The measurements of the mechanical strength of the lyophilized products were carried out with a needle penetrometer usually employed for measuring the hardness of tablets. An increasing force is applied to the material over a constant surface area and the force required for breakage or for penetration of the needle is measured.

For the products No. 1 to No. 5 quoted above, the following hardnesses were found:

No. 1—too low, not measurable
No. 2 — 5.5 to 7 kg
No. 3 — 8 to 12 kg
No. 4 — 2 to 3 kg
No. 5 — 6 to 7 kg.

TABLE II

Temperature and pressure conditions used during the lyophilization process

Time in hours	0	2	3	4	5	6	20	22	24	25	27	28	29	30	31	44	46
Temperature of the material in °C.	+20°	+5°	0°	−4°	−24°	−30°	−24°	−22°	−15°	−1°	+22°	+25°	+27°	+28°	+30°	+44°	+37°
Pressure in mm of Hg	760	760	760	760	2×10^{-1}	2×10^{-1}	1.3×10^{-1}	1.3×10^{-1}	1.3×10^{-1}	1.3×10^{-1}	10^{-1}	10^{-1}	10^{-1}	10^{-1}	3×10^{-3}	3×10^{-3}	

TABLE III

Water uptake of the various samples as a function of time

	No. 1		No. 2		No. 3		No. 4		No. 5		*	**
	Liver alone		Glycine		Lactose		Glycine + Liver		Lactose + Liver			
Weight of the lyophilized product	2.30 g		61 g		61 g		63.3 g		63.3 g			
15 mins	20 mg	0.87%	13mg	0.021%	13mg	0.021%	20mg	0.031%	16mg	0.025%	7mg	3mg
30 mins	34	1.48	23	0.038	23	0.038	37	0.058	27	0.042	14	4
45 mins	45	1.96	30	0.049	30	0.049	51	0.072	36	0.057	21	6
60 mins	55	2.4	36	0.059	37	0.060	60	0.09	44	0.070	24	7
2 hrs	94	4.1	58	0.095	59	0.091	92	0.145	68	0.107	34	9
3 hrs	112	4.9	68	0.112	71	0.116	107	0.17	82	0.129	39	11
4 hrs 15 mins	131	5.7	78	0.128	86	0.14	130	0.20	97	0.153	52	11
5 hrs 30 mins	153	6.65	88	0.144	100	0.164	152	0.24	116	1.183	64	16
6 hrs 15 mins	164	7.1	92	0.151	102	0.167	165	0.26	126	0.20	73	24
24 hrs	249	10.9	108	0.178	154	0.252	285	0.45	235	0.37	177	81
72 hrs	317	13.8	114	0.188	165	0.270	387	0.61	334	0.52	273	169

* Water uptake by the liver extract in the glycine (No. 4 - No. 2)

** Water uptake by the liver extract in the lactose (No. 5 - No. 3)

Example 2

The process described in Example 1 is repeated, but replacing the gum arabic by each of the following colloidal substances.

The experiments were carried out adding the amount of colloidal substance indicated below to 250 g. of lactose or of glycine.

Polyethylene glycol M.W.=20,000	15 g.
Polyethylene glycol M.W.= 6,000	15 g.
Polyvinylpyrrolidone	10 g.
Sodium carboxymethylcellulose	2.5 g.
Sodium alginate	1.25 g.
Guaranate AC 110	1.25 g.

All these experiments proved satisfactory and gave results of the same order as those mentioned in Example 1 above.

Example 3

The process of Example 1 is repeated, but replacing the lactose and the glycine by sucrose or mannitol, or by a combination of glycine and glucose. The experiments carried out with gum arabic gave good results. Table IV below gives in grams the quantities used in the various experiments.

TABLE IV

Experiment	1	2	3
Glycine	100		
Mannitol		250	
Sucrose			250
Glucose	250		
Gum arabic	15	15	15

Example 4

This Example describes the preparation of a medicine based on Vitamin C.

The mixture is created into a foam so as to cause the existence of small channels which permit lyophilisation, and the vitamin C is introduced into the mixture at the last moment so that it virtually does not dissolve.

Experiments carried out on the following mixtures: (1) lactose+glycine+gum arabic; (2) glycine+gum arabic; did not allow a dose of 0.05 g. of vitamin C to be exceeded, regardless of the technique employed to cause foaming.

However, on using the following mixture: glycine+gum arabic+RC 102 (Pluronic F 68) in which the RC 102 (a block polymer of ethylene oxide, propylene oxide and ethylene glycol) serves as a foam stabiliser, it proved possible successfully to lyophilise doses of vitamin C of 0.100 g., 0.250 g. and 0.500 g. "Pluronic" is a registered Trade Mark.

TABLE V

Formulations produced

Vitamin C	0.100 g.	0.250 g.	0.500 g.
Glycine	1.100 g.	1.100 g.	1.100 g.
Gum arabic	0.06 g.	0.06 g.	0.06 g.
RC 102 platelets	0.05 g.	0.05 g.	0.05 g.
De-ionized water	0.3 ml.	0.3 ml.	0.3 ml.
For one piece of approximate weight	1.31 g.	1.46 g.	1.71 g.

Example 5

This Example describes the preparation, by lyophilisation, of a medicine based on arginine acid aspartate in an effervescent form. The following two mixtures A and B are separately prepared in a mortar.

Mixture A	
Sodium bicarbonate	8 g.
Arginine base	4.34 g.
Sucrose	6.66 g.
Lactose	6 g.
Water	1.5 ml.
Mixture B	
Citric acid	5 g.
Aspartic acid	5.66 g.
Sucrose	7.34 g.
Lactose	7 g.
Water	1.5 g.

The two mixtures A and B are separately cooled until they reach a temperature of −4°C. or below. A is then rapidly mixed with B while continuing cooling, and an appropriate amount of a colloidal substance mentioned in Example 2 is added. The paste is spread as an approximately 1 cm thick layer on metal plates and frozen at −20°C., and the material is lyophilized. The lyophilized product is then cut into pieces each weighing 5 g. Each piece contains 1 g. of arginine acid aspartate and dissolves very rapidly in water.

WHAT WE CLAIM IS:—

1. Process for producing a lyophilized pharmaceutical composition which comprises mixing a medicament selected from liver extracts, vitamin C and arginine acid aspartate, in the presence of water with a lyophilization adjuvant comprising (a) at least one substance selected from non-toxic hydrophilic colloids, polysaccharides and polymers of high molecular weight capable of yielding aqueous colloidal solutions, and (b) at least one water-soluble, edible, crystallisable, physiologically innocuous filler, and lyophilizing the mixture obtained.

2. Process according to claim 1 in which the lyophilization adjuvant comprises (a) at least one substance selected from gum arabic, alginates, pectinates, polyvinylpyrrolidone, polyethylene glycols and sodium carboxymethylcellulose, and (b) at least one of lactose, glycine, mannitol, sorbitol, glucose and sucrose.

3. Process according to claim 1 in which the medicament is a liver extract and the lyophilization adjuvant comprises a mixture of gum arabic and glycine, or a mixture of gum arabic and lactose.

4. Process according to claim 1, 2 or 3 in which a mixture of 4 parts of liver extract, 15 parts of water, 1 part of gum arabic, and 60 parts of glycine or of lactose, the said parts being by weight, is lyophilized.

5. Process according to claim 1 or 2 in which the medicament is vitamin C, and the mixture to be lyophilized includes additionally a substance capable of maintaining the vitamin and lyophilization adjuvant — when intimately mixed together in the presence of water—in the form of a foam, and the mixture is converted into a stable foam before lyophilization.

6. Process according to claim 1 or 5 in which the medicament is vitamin C and the lyophilization adjuvant comprises a mixture of gum arabic and glycine.

7. Process according to claim 5 or 6 in which the mixture of vitamin C, lyophilization adjuvant and water is converted into a foam stabilized by a polymer of molecular weight between 7500 and 8250 of the formula:

$$HO(C_2H_4O)_x(C_3H_6O)_yC_2H_4O)_zH$$

(wherein x, y and z are integers) in which the $(C_3H_6O)_y$ portion has a molecular weight of 1500 to 1800, and the $(C_2H_4O)_{x+z}$ portion represents 80—90% by weight of the polymer.

8. Process according to claim 5, 6 or 7 in which the mixture to be lyophilized contains 0.1 to 0.5 parts of vitamin C, 0.3 part of water, 1.1 part of glycine, 0.06 part of gum arabic, and 0.05 part of a polymer of the formula specified in claim 7, the said parts being by weight.

9. Process according to claim 1 in which a mixture, capable of producing effervescence, consisting of a non-toxic organic acid and, as base, a mineral carbonate or bicarbonate is added to the mixture to be lyophilized at a temperature below 0°C. and sufficiently low to prevent any reaction between the said acid and carbonate or bicarbonate.

10. Process according to claim 9 in which the non-toxic acid is citric, tartaric or ascorbic acid, and the base is an alkali metal carbonate or bicarbonate or an alkaline earth metal carbonate or bicarbonate.

11. A process according to claim 1, 9 or 10 in which the medicament is arginine acid aspartate and the water-soluble, edible, crystallisable, physiologically innocuous filler is a mixture of lactose and sucrose.

12. Process according to claim 9, 10 or 11 in which a mixture of citric acid and sodium bicarbonate is added to the mixture to be lyophilized.

13. Process according to claim 1 substantially as described in any one of the foregoing Examples.

14. Lyophilized pharmaceutical compositions when produced by the process claimed in any one of the preceding claims.

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